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PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Antitussive Medicament with Prolonged Effect

We, MEAD JOHNSON & COMPANY. a Corporation organized under the laws of the State of Indiana United States of America, of Evansville, Indiana, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to carrageenan complexes of the antitussive opium alkaloids such as codeine containing from 1 to 10 parts by weight of carrageenan per part by weight of alkaloid which are formed in aqueous solutions at temperatures of 40° to 60°C. Prolongation of the antitussive effect is achieved.

Therapeutic interest in preparations which liberate their active principles progressively and hence exercise a prolonged effect on the patient is well known. Such preparations are especially interesting in the antitussive field. A considerable body of prior art in the field of prolonged action dosage forms has accumulated. These forms generally rely on the use of impervious coatings for the active medicament which are eroded slowly and at a predetermined rate after ingestion, or upon the leaching of the active medicament from an indigestible matrix. Another way that has been used in the prior art to obtain prolonged drug action is by means of ion exchange resin absorbates of the drug in which the drug is gradually eluted from the resin by digestic juices.

The invention deals with antitussive compositions containing known antitussive bases including the opium alkaloids of established antitussive value, and their synthetic derivatives and analogs. The present compositions are formulated to provide a prolonged effect. They are characterized by the fact that the active principle is composed of the complex formed between an antitussive base and a sulfated poly-saccharide of the carrageenan group as hereinafter defined.

Antitussive bases which can be advantageously combined as complexes according to the present invention include the opium alkaloids and their synthetic derivatives and analogs of known antitussive activity. These include morphine, codeine, noscapine, their synthetic derivatives such as the N-oxides, derivatives resulting from alkylation, esterification, reduction, or rearrangement thereof such as pholcodine, ethylmorphine, diacetylmorphine, dihydromorphinone, dihydrocodeinenone, and synthetic analogs thereof such as dextromethorphan.

As used herein "sulfonated polysaccharide" means a sulfated polysaccharide selected from the group of carrageenans which are obtainable from plants like, for example, Irish moss (Chondrus crispus (L.)). Various known materials of this type are described in Ullmann, "Enzyklopaedie des Technischen Chemie" (3rd ed., Vol. 13, pps. 186—187). Particular reference is made in the following disclosure, however, to the Chondrus extract known as carrageenan.

According to the present invention there is provided an antitussive complex of a sulfated polysaccharide as hereinbefore defined and a base selected from the opium alkaloids and their synthetic derivatives and analogs known to have antitussive activity, said complex being formed by contacting a water soluble acid addition salt of said base with an aqueous solution containing from 1 to 10 parts by weight of said sulfated polysaccharide per part by weight of said base at a temperature of 40—60°C.

The present invention also provides an antitussive complex composition containing in each dosage unit an effective amount of complex of a sulfated polysaccharide as hereinbefore defined and an antitussive base selected from the opium alkaloids and their synthetic

derivatives and analogs known to have antitussive activity in the presence of a diluent, said complex being formed by contacting a water soluble acid addition salt of said base with an aqueous solution containing from 1 to 10 parts by weight of said sulfated polysaccharide per part by weight of said base at a temperature of 40—60°C.

Although it is not possible to characterize the complexes of the type envisaged by the invention by means of a formula, it is nevertheless known that these materials constitute definite chemical species with individual properties distinct from those of their constituents. Evidence of their existence as distinct entities is set out in the following paragraphs.

When an aqueous solution of carrageenan is put in contact with an aqueous solution of an antitussive base salt of the type referred to above, there is a reaction between the polyanion of the polysaccharide and the cation of the base salt. This combination of the two components is evident by a change in the physical properties of the solution. The appearance of turbidity measured by nephelometry or of a precipitate. Thus, when 1 ml. of a 5% aqueous solution of noscapine hydrochloride is added to 10 ml. of a 1% solution of carrageenan, an abundant flocculent precipitate of the corresponding complex is rapidly formed.

Another method of characterizing the complexes is by dialysis. When an aqueous solution of carrageenan contained in a dialysis bag made of a semipermeable membrane is placed in an aqueous solution of a salt of the antitussive base, after a few hours it can be observed that the concentration of the base in a solution outside the dialysis bag has diminished as a result of dialysis of the salt into the bag and progressive fixation thereof by the polysaccharide solution.

The existence of the complexes as distinct entities is also manifested by their remarkable pharmacological and therapeutic properties. These are described below.

The method of preparing the sulfated polysaccharide-antitussive base complexes involves reacting the components with each other in warm aqueous solution. For example, a water soluble acid addition salt of the selected antitussive base is dissoved in a dilute aqueous solution of carrageenan having a concentration of up to 3% (preferably 1 to 3%) and containing from 1 to 10 parts by weight of carrageenan per part by weight of the selected antitussive base. A solution of the antitussive base salt having any convenient concentration may be first prepared and mixed with the carrageenan solution to effect contact of the reactants. The reaction is conducted at elevated temperature in the interest of shortening the reaction time, but it is important not to employ a temperature sufficiently high to result in hydrolysis of the polysaccharide. Temperatures if 40° to 60°C. are operable, and temperatures in the range 45° to 50°C. are preferred. Reaction periods sufficient to effect intimate contact and reaction are employed. A period of 1 hour is usually adequate.

The complex is recovered from the reaction solution by evaporation, or by freezing and drying from the frozen state. Solvent precipitation employing a water-miscible organic solvent in which the carrageenan complex is insoluble may also be employed. Examples of such solvents are isopropanol and acetone. In recovering the complex by evaporation, vacuum evaporation is preferred in order to achieve a satisfactory rate of solvent removal and yet maintain the solution temperature below 60°C.

The resulting complex contains from 9 to 50% by weight of the antitussive base when prepared from 1 to 10 parts by weight of carrageenan per part by weight of said base. The preferred complexes of the present invention contain from 30 to 35% by weight of the antitussive base and are prepared from approximately 2 parts by weight of the sulfated polysaccharide per part by weight of antitussive base.

Pharmacological Properties

Acute toxicity measurements at various time intervals following oral administration of the codeine-carrageenan complex prepared as described in Example 2 in comparison with the corresponding values determined with an equivalent quantity of codeine phosphate, show the prolonged effect of the complex. The values calculated by the Kaerber-Berhens method and expressed as mg. of codeine base per kg. of animal are the following.

Toxicity Values of Codeine-Carrageenan Complex Compared to Codeine Phospate.

	Time after administration			
	15 min.	30 min.	60 min.	24 hours
codeine phosphate	312	317.5	307.5	307.5
codeine-carrageenan complex	398.5	333.5	316	316

It can be seen that the maximum effect is essentially reached in 15 min. in the case of codeine phosphate and only after 1 hour in the case of the complex. Further toxicity

measurements indicate that the maximum dose tolerated with no deaths during 24 hours is 150mg./kg., calculated on the basis of codeine base contained in the complex. The minimum lethal dose (LD_{100}) is 500 mg./kg., expressed as codeine base.

The relationships between acute toxicities of the known salts of the other antitussive bases envisaged by the present invention and those of the complexes forming the object of the present invention are analogous to those reported for codeine. Chronic toxicity experiments have demonstrated entirely satisfactory tolerance of the complexes in doses 10 times the therapeutic dose.

The antitussive properties of the complexes are manifested at the same doses, expressed as the base, as for the simple salts, such as the hydrobromide, hydrochloride, citrate, but the activity is prolonged. This is illustrated by an experiment in which 10 mg./kg. of noscapine in the form of hydrochloride administered orally was compared with the effect of an equivalent dose of the noscapine-carrageenan complex described in Example 1 in guinea pigs exposed to the action of SO_2 vapor. Noscapine hydrochloride was effective when administered from 1 to 2 hours before exposure of the animal to the irritant agent, but its effect was doubtful when administered 3 hours prior to challenge and after 3 hours there was no effect. With the noscapine-carrageenan complex, the antitussive action was still evident 5 hours after administration of the drug orally.

Another feature of clinical interest and which contributes to the characterization of the complexes is the fact that the pharmaceutical preparations made with antitussive base-polysaccharide complexes do not have the bad taste for which the opium alkaloids are noted.

Preferred complexes are those of codeine, noscapine, and pholcodine.

Description of Preferred Embodiments:

EXAMPLE 1

A solution of 100 g. of carrageenan (Aubygum X2 of the Auby Company) in 5 l. of water is prepared by heating to 45—50°C. with stirring. There is added slowly, with stirring, a solution of noscapine hydrochloride corresponding to 50 g. of the base (55—60 g., depending upon the hydrochloride content). The mixture is stirred and kept at 45—50°C. for 1 hour, and is then evaporated to dryness *in vacuo* at a temperature below 50°C. There is thus obtained a resinous mass which is ground and sifted to produce a powder whose content of base is approximately 30% by weight.

EXAMPLE 2

By the procedure indicated in Example 1, and starting with 100 g. of carrageenan and 62 g. of codeine hydrochloride, the carrageenan-codeine complex is obtained.

EXAMPLE 3

The carrageenan-ethylmorphine complex is prepared by the procedure indicated in Example 1, starting from 100 g. of carrageenan and 61.5 g. of ethylmorphine hydrochloride.

EXAMPLE 4

A solution of 100 g. of carrageenan in 5 l. of water is prepared by warming to 45°C. There is added in small portions, with continuous stirring, a solution of 52 g. of crystalline pholcodine base in 500 ml. of water and 20 ml. of concentrated hydrochloric acid. The mixture is stirred for 1 hour at 45°C. It is then evaporated *in vacuo*, ground and sieved. The complex is thus obtained in solid form.

Complexes of the other antitussive bases referred to by adaptation of Example 1.

The complexes prepared in the foregoing fashion may be formulated into liquids for oral use or into the solid compositions such as compressed tablets and gelatin capsules. This is illustrated in the examples which follow. Although the basic antitussive combination may only contain the complex of a sulfated polysaccharide of the carrageenan group and one particular antitussive base, several complexes may be combined advantageously in the composition. Such a composition of complexes would include for example the carrageenan-codeine complex. Preferred combinations employ carrageenan-noscapine complex as one component with one of the other base complexes listed above as the second component. The use of a combination of such antitussive ingredients results in a synergistic effect due to the peripheral action of the noscapine and the central action of the second antitussive base. The total amount of carrageenan antitussive base complex employed in a given daily dose corresponds to that recognised as effective by current medical practice. Where two or more complexes are employed, the dose of each is reduced so that the total dose employed corresponds to the recognized dosage. They are employed in the ratio of from 2 to 3 parts of noscopine to 3 to 2 parts of the second base, or stated another way, from 2/3 to $1\frac{1}{2}$ parts by weight of noscapine per part by weight of the second antitussive base is employed in the combination dosage products. A preferred composition contains 3 parts by weight noscapine and 2 parts by weight codeine. In another preferred composition, a daily dosage unit thereof contains carrageenan complex equivalent to 45 mg. of noscapine base and 30 mg. of codeine base.

EXAMPLE 5

Preparation of a "drinkable" suspension of the carrageenan-codeine and carrageenan-noscapine complexes:

carrageenan-noscapine complex (expressed as base)	150	mg.
carrageenan-codeine complex (expressed as base)	100	mg.
gum tragacanth (thickening agent)	0.40	g.
citric acid (flavouring agent)	0.685	g.
sodium cyclohexylsulfamate (sweetening agent)	0.30	g.
methyl para-hydroxybenzoate (preservative)	0.08	g.
propyl para-hydroxybenzoate (preservative)	0.04	g.
sorbiton (excipient)	60	g.
95% ethyl alcohol (preservative)	3	ml.
orange essence	2	ml.
distilled water q.s.	100	ml.

The preparation of the above formulation is effected thus:

A gel of gum tragacanth containing the preservatives is prepared by dispersing and homogenization. To this mass there is added a solution of the sodium cyclohexylsulfamate and the citric acid. To this mixture the sorbitol and then the aromatic agents are added and the alkaloid complexes are carefully dispersed therein. The resulting mixture must be agitated before use.

A coffee-spoonful of this suspension corresponds to 5 mg. of codeine and 7.5 mg. of noscapine.

A syrup can be prepared in the same way by making a solution of the carrageenanate and omitting the gum tragacanth.

EXAMPLE 6

Preparation of gelatin capsules:

	For one capsule:	
carrageenan-noscapine complex (expressed as base)	7.5	mg.
carrageenan-codeine complex (expressed as base)	5	mg.
lactose	25	mg.
starch	10	mg.
talc q.s.	50	mg.

The powders are mixed after sifting and filled into capsules.

EXAMPLE 7

Preparation of compressed tablets:

	For one tablet:	
carrageenan-noscapine complex (expressed as base)	7.5	mg.
carrageenan-codeine complex (expressed as base)	5	mg.
lactose	60	mg.
gelatin	1	mg.
potato starch	20	mg.
talc	5	mg.
magnesium stearate q.s.	100	mg.

An intimate mixture of the powders is moistened with an aqueous solution of the gelatin, granulated, and dried; after grinding, it is lubricated by addition of the talc and the magnesium stearate, and then compressed in units of 100 mg. The compressed tablets thus obtained can be coated by the usual coating procedures.

EXAMPLE 8

Solution for Drops:

carrageenan-noscapine complex (expressed as base)	1.50	g.
carrageenan-codeine complex (expressed as base)	1	g.
glycerin	50	g.
aromatics	5	g.
95% alcohol	20	ml.
distilled water q.s.	100	ml.

The complexes are dissolved in part of the distilled water, then the glycerin and aromatics are added, and the solution is made up to volume.

The therapeutic effects by the complexes covered in the invention have been confirmed by clinical trial, as is shown, for example, by the following case:

Case No. 5

Mr. Paul D. . ., 48 years old, had a spasmodic cough following grippal bronchitis. This cough occurred chiefly at night, but also during the day.

He was treated for approximately one month with various classical antitussive agents in the form of tablets, but the cough remained refractory.

He was then treated with the codeine-noscapine syrup following Example 5, at a dose of 2 desert-spoonfulls in the morning, at noon, and at bedtime.

After 5 days of treatment the cough was controlled and the dosage could be reduced to 2 spoonfulls morning and evening, and then to 1 spoonful at evening.

Treatment was carried out for 12 days without the appearance of any gastric or intestinal intolerance.

The cough disappeared without the occurrence of secondary effects.

The average dose of the medicament as ascertained by the clinical investigation, is established as equivalent to 30mg./day of codeine base of 45 mg./day of noscapine.

The indications for the medicament are comparable to those of the known antitussives from which the products covered by the invention are derived, i.e., coughs of any nature, the new therapeutic result supplied by these complexes consisting essentially in the prolonged effect.

While several particular embodiments of this invention are shown above, it will be

understood, of course, that the invention is not to be limited thereto, since many modifications may be made, and it is contemplated, therefore, by the appended claims, to cover any such modifications as fall within the scope of this invention.

WHAT WE CLAIM IS:—

1. An antitussive complex of a sulfated polysaccharide as hereinbefore defined and a base selected from the opium alkaloids and their synthetic derivatives and analogs known to have antitussive activity, said complex being formed by contacting a water soluble acid addition salt of said base with an aqueous solution containing from 1 to 10 parts by weight of said sulfated polysaccharide per part by weight of said base at a temperature of 40—60°C.

2. The complex as in claim 1, wherein said complex is formed in aqueous solution having a concentration of up to 3% by weight of carrageenan.

3. The complex as in claim 1 or 2, wherein said antitussive base is morphine, codeine, noscapine, pholcodine, ethylmorphine, diacetylmorphine, dihydromorphine, dihydrocodeinone, or dextromethorphan.

4. An antitussive complex composition containing in each dosage unit an effective amount of complex of a sulfated polysaccharide as hereinbefore defined and an antitussive base selected from the opium alkaloids and their synthetic derivatives and analogs known to have antitussive activity in the presence of a diluent, said complex being formed by contacting a water soluble acid addition salt of said base with an aqueous solution containing from 1 to 10 parts by weight of said sulfated polysaccharide per part by weight of said base at a temperature of 40—60°C.

5. The composition of claim 4, wherein said complex is formed in aqueous solution having a concentration of up to 3% by weight of carrageenan.

6. The composition of claim 4 or 5, wherein said antitussive base is morphine, codeine, noscapine, pholcodine, ethylmorphine, diacetylmorphine, dihydromorphinone, dihydrocodelinone, or dextromethorphan.

7. The composition of claim 6, wherein said complex contains frim 9 to 50% by weight of said base.

8. The composition of claim 6, wherein said complex contains from 30 to 35% by weight of said base.

9. The composition of claim 6, wherein a combination of noscapine and one of said other bases is employed in the proportion of from 2/3 to $1\frac{1}{2}$ parts by weight noscapine per part by weight of said other base.

10. The composition of claim 9, wherein said other base is codeine.

11. The composition of claim 8, containing 3 parts by weight noscapine and 2 parts by weight codeine.

12. The composition of claim 9, wherein a daily dosage unit thereof contains carrageenan complex equivalent to 45 mg. of noscapine base and 30 mg. of codeine base.

13. An antitussive complex substantially as herein described with particular reference to the Examples.

14. An antitussive complex composition substantially as herein described with particular reference to the Examples.

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